BASIC SCIENCE REVIEW

MYOCYTE CONTRACTILE DYSFUNCTION WITH HYPERTROPHY AND FAILURE: RELEVANCE TO CARDIAC SURGERY

C. Allyson Walker, BA
Fred A. Crawford, Jr, MD
Francis G. Spinale, MD, PhD

Despite significant improvements in the intraoperative management of patients undergoing cardiac surgery, postoperative left ventricular (LV) pump dysfunction occurs and often requires inotropic and/or vasodilator therapy. This LV pump dysfunction can contribute to a complex postoperative course.[1,2] It is likely that the number of cardiac surgical procedures, such as coronary artery bypass grafting (CABG), will increase in the future due to several factors. First, the relative number of patients surviving an initial myocardial infarction and the relative proportion of elderly patients have both increased and therefore may ultimately require CABG.[3] The purpose of this review is to place these conditions in the context of cardiac surgery with particular emphasis on the ischemia/reperfusion injury that may occur during the intraoperative period. Although a number of systemic and neurohormonal factors clearly influence LV pump function and hemodynamics in the postoperative setting, this review will focus on basic systems within the cardiac myocyte that are altered in hypertrophy and/or failure, which may in turn influence contractility in the perioperative setting. This review will be a structure-function presentation in which the myocyte will be dissected into key structural components that are directly related to contractile performance.

Sarcolemmal systems

The sarcolemma contains channels and energy-dependent pumps that play a fundamental role in both the generation of the action potential and excitation-contraction coupling. The most common electrophysiologic abnormality is a prolongation of the action potential. A representative action potential from a normal and failing human myocyte is shown in Fig 1. Membrane repolarization is initiated by the K^+ efflux of the delayed rectifier current, which is later joined by an additional outward K^+ current to return the sarcolemma to the resting membrane potential.[4] The prolongation of the action potential with hypertrophy and/or failure is likely due to alterations in key sarcolemmal channels and currents that contribute to the action potential repolarization. Specifically, the delayed rectifier current, which is directly responsible for repolarization, is reduced in myocardial hypertrophy[5,6] and has been associated with a prolongation of the action potential.[7,8] With the use of gene transfection techniques, enhanced production of K^+ channels that contribute to the delayed rectifier current has been shown to correct action potential prolongation.[9] This observation supports the ionic basis for changes in action potential morphology, including defects in K^+ currents that are operable during action potential repolarization. The prolongation of the action potential in hypertrophy and/or failure may result in early depolarization, which may create a re-entry circuit, thereby promoting arrhythmias.[10,11] The Na^+/K^+ adenosine triphosphatase (ATPase), which contributes to the maintenance of the resting action potential, is altered in severe hypertrophy and/or failure[12-14] and may contribute to a more positive and unstable resting potential. These molecular defects that contribute to changes in the action potential with hypertrophy and/or failure may have particular relevance to the development of ventricular arrhythmias after cardiac operations.[15]

Excitation-contraction coupling

Normal myocyte contraction depends on a highly organized sequence of molecular and mechanical events between the sarcolemma, the sarcoplasmic reticulum (SR), and the contractile apparatus. After sarcolemmal

From the Division of Cardiothoracic Surgery, Medical University of South Carolina, Charleston, SC.

Received for publication Sept 3, 1999; revisions requested Sept 23, 1999; revisions received Oct 19, 1999; accepted for publication Oct 21, 1999.

Address for reprints: Francis G. Spinale, MD, PhD, Cardiothoracic Surgery, Room 625, Strom Thurmond Research Building, 770 MUSC Complex, 114 Doughty St, Charleston, SC 29425.

J Thorac Cardiovasc Surg 2000;119:388-400

0022-5223/2000 $12.00 + 0 **12/1/104038**

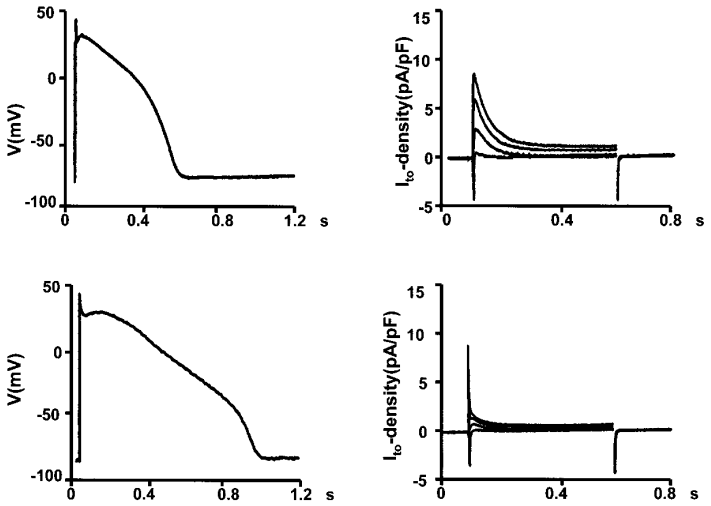

Fig 1. The action potential *(left panels)* and transient outward K^+ current *(right panels)* of normal *(top)* and failing *(bottom)* human ventricular myocytes. A common abnormality associated with myocyte hypertrophy and/or failure is a prolongation of the action potential. The transient outward K^+ current density *(I_{to})* was reduced in failing human myocytes. A reduction in key K^+ currents involved in sarcolemmal repolarization likely contributes to action potential prolongation in hypertrophy and/or failure. *V*, Voltage; *pA/pF*, picoamps/picofarads. (From Tomaselli GF, Beuckelmann DJ, Calkins HG, Berger RD, Kessler PD, Lawrence JH, et al. Sudden cardiac death in heart failure: the role of abnormal repolarization. Circulation 1994;90:2534-9. Reprinted with permission of Lippincott Williams & Wilkins.)

depolarization, the L-type Ca^{2+} channel becomes activated, resulting in a Ca^{2+} current across the sarcolemma, which activates the calcium release channels of the SR, as shown in Fig 2. After calcium release channel activation, a bolus release of Ca^{2+} from the SR engages the myofilament apparatus, resulting in sarcomere shortening. The return to resting sarcomere length is an energy-dependent process that has been termed active relaxation.[4] Active relaxation primarily consists of the re-uptake of intracellular Ca^{2+} by SR Ca^{2+} ATPase (SERCA-2), thus reducing the concentration of intracellular Ca^{2+}. For the purposes of this review, specific alterations in excitation-contraction coupling that occur in hypertrophy and/or failure will be divided into two events: contraction and active relaxation.

Contraction. Since Ca^{2+} influx through the L-type Ca^{2+} channel is the initial trigger for excitation-contraction coupling, a defect in function and/or density will alter myocyte contractility.[16,17] Accordingly, the function of the L-type Ca^{2+} channel has been the focus of several investigations.[17-20] The majority of these studies have reported a reduction in L-type Ca^{2+} current and/or channel density in hypertrophied and/or failing myocytes. For example, Mukherjee and associates[16] reported a decrease in L-type Ca^{2+} current that was associated with intrinsic defects in contractile function with the development of pacing-induced heart failure. The peak levels of Ca^{2+} released into the cytosolic compartment have been demonstrated to be decreased in severe hypertrophy and/or failure.[21] The Ca^{2+} discharged from the SR binds to troponin C, resulting in conformation changes of the contractile apparatus. These changes allow for myofilament cross-bridge formation and, thus, myocyte shortening. A decrease in SR Ca^{2+} release would inhibit the ability of the myofilament apparatus to undergo the conformational changes necessary for cross-bridge formation. Second, the absolute reduction of Ca^{2+} will result in a diminished number of cross-bridges formed during a contractile cycle, leading to diminished contractile force generation. Several mechanisms may be responsible for the reduced release of Ca^{2+}. First, there appears to be a reduction in the trigger Ca^{2+} current marked by L-type Ca^{2+} channel dysfunction. Second, SR calcium release channels appear to be reduced[22,23] or dysfunctional[24,25] in severe hypertrophy and/or failure. A summary of the alterations in Ca^{2+} dynamics that occur in myocyte hypertrophy and/or failure appears in Fig 2.

The fundamental contractile unit of the myocyte is the sarcomere. The sarcomere is composed of actin and myosin filaments, tropomyosin, and the troponin complex: troponin C, troponin I, and troponin T. Although a

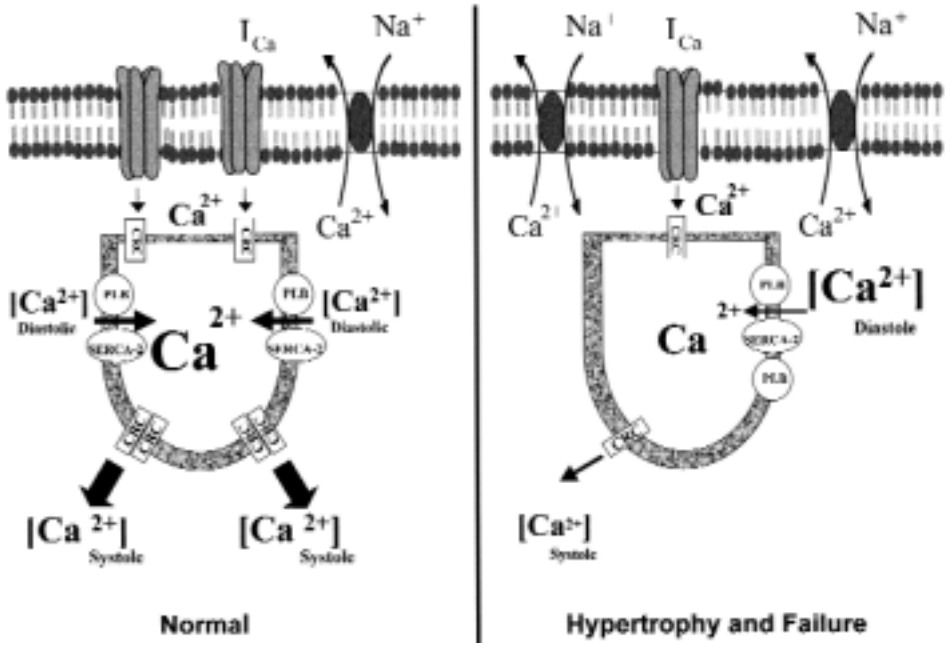

Fig 2. A schematic of key alterations that can contribute to abnormal excitation-contraction coupling in the hypertrophied and/or failing myoctye. In the normal myocyte *(left)*, sarcolemmal depolarization results in a trigger Ca^{2+} *(I_{ca})* current through the L-type channel, which activates a bolus release of Ca^{2+} from the SR calcium release channels *(CRC).* The increased cytosolic Ca^{2+} causes conformational changes in the myofilament apparatus, which results in cross-bridge formation and sarcomere shorting. Active relaxation consists of Ca^{2+} re-uptake into the SR by SR Ca^{2+} ATPase *(SERCA-2).* The rate of SR Ca^{2+} uptake is influenced by the SERCA-2 regulatory protein phospholamban *(PLB).* Cytosolic Ca^{2+} concentrations can be further reduced through the slower actions of the sarcolemma Na^+/Ca^{2+} exchanger and a sarcolemmal Ca^{2+} ATPase (not shown). Alterations in the expression and/or function of key components of the excitation-contraction coupling process may affect Ca^{2+} handling and homeostasis with severe hypertrophy and/or failure *(right).* There is a reduction in the L-type Ca^{2+} current and/or expression, which can result in a blunted trigger Ca^{2+} current and thereby reduce the release of Ca^{2+} through the CRC. A reduction in SERCA-2 expression and function have been reported in severe hypertrophy and/or failure, which would result in two consequences. First, a reduction in SERCA-2 would result in a reduced capacity for SR CA^{2+} re-uptake. Second, stoichiometric alterations between SERCA-2 and PLB would result in reduced SERCA-2 sensitivity to Ca^{2+}. The slowed removal of Ca^{2+} from the intracellular compartment would result in an increase in diastolic Ca^{2+}. Furthermore, the Na^+/Ca^{2+} exchanger is up-regulated, presumably as a compensatory mechanism (albeit slower) to remove cytosolic Ca^{2+} levels.

myosin isoform switch was previously considered to occur only in animal models of failure,[26-29] a recent study has identified that it occurs in the failing human myocyte. Specifically, Lowes and associates[30] have reported a reduction in the expression of the cardiac specific α-myosin heavy chain coupled with a reciprocal increase in the expression of the β-myosin heavy chain in severe hypertrophy and failure.[30] The β isoform of the myosin heavy chain causes a slower velocity of shortening when compared with the α-myosin heavy chain.[31] Therefore, these changes in myosin heavy chain expression with severe hypertrophy and/or failure may directly contribute to alterations in LV ejection performance. Although there appears to be no change in cardiac troponin I in the setting of hypertrophy and/or failure, its presence in the serum has been used as a marker for acute myocardial ischemia.[32] Interestingly, it appears that CABG coupled with cardiopulmonary bypass can be associated with the release of cardiac troponin I.[33] The transient loss of troponin I in cardiac myocytes after CABG may further exacerbate contractile dysfunction in the setting of hypertrophy and/or failure.

While studies regarding the contractile apparatus in the setting of severe hypertrophy and/or failure are currently ongoing, in general terms the myofilament apparatus appears to be structurally intact. In contrast, the intracellular environment that surrounds the contractile elements is substantially abnormal in the setting of hypertrophy and/or failure and is likely to be a major contributory cause of LV contractile dysfunction.

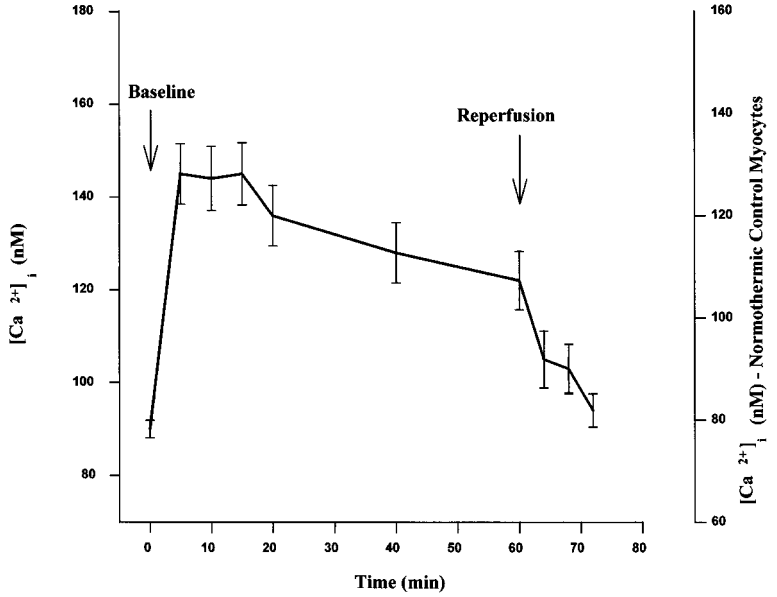

Fig 3. Intracellular free Ca^{2+} levels of normal myocytes before and after simulated hyperkalemic cardioplegic arrest and rewarming. Intracellular Ca^{2+} levels increased from baseline as cardioplegic arrest was induced, and the increase persisted through the early reperfusion period. The increased intracellular Ca^{2+} induced by the depolarizing cardioplegic arrest may have particular relevance in the setting of hypertrophy and/or failure. (From Dorman BH, Hebbar L, Clair MJ, Hinton RB, Roy RC, Spinale FG. Potassium channel opener–augmented cardioplegia: protection of myocyte contractility with chronic left ventricular dysfunction. Circulation 1997;96[9 Suppl]:II253-9. Reprinted with permission of Lippincott Williams & Wilkins.)

Active relaxation. The resequestration of Ca^{2+} into the SR occurs primarily through the actions of SERCA-2 and the influence of the regulatory protein phospholamban. The regulatory influence of phospholamban on SERCA-2 is dependent on the phosphorylation state. When phosphorylated, phospholamban enhances SERCA-2 Ca^{2+} affinity and uptake, whereas dephosphorylated phospholamban diminishes SERCA-2 Ca^{2+} function. Defects in the resequestration of Ca^{2+} into the SR have been clearly identified in severe hypertrophy and/or failure, which is manifested by increased intracellular diastolic Ca^{2+}.[34-37] At the myocardial level, defects in Ca^{2+} homeostasis will result in a slowed LV myocardial relaxation. Furthermore, defects in SR Ca^{2+} re-uptake would result in increased diastolic Ca^{2+} concentrations, which, in turn, cause decreased sensitivity of the contractile apparatus to intracellular Ca^{2+} concentrations. Alterations in Ca^{2+} resequestration that occur in severe hypertrophy and/or failure are likely due to several factors. The majority of studies have reported decreased protein expression and/or function of SERCA-2 in severe hypertrophy and/or failure.[38-42] For example, Hasenfuss and associates[41] reported a 36% reduction in SERCA-2 protein levels in the failing human myocardium. In a recent study by Dillman,[43] cardiac myocytes were transfected with DNA for SERCA-2, which resulted in increased synthesis and protein levels. The enhanced protein expression of SERCA-2 in this study increased Ca^{2+} re-uptake.[43] This in vitro study emphasizes the importance of the loss of expression and function of SERCA-2 on Ca^{2+} homeostasis. Although it appears that SERCA-2 is reduced in severe hypertrophy and/or failure, the changes in the regulatory protein phospholamban appear to be more complex. In animal models of hypertrophy and failure, a reduction in the expression of phospholamban has been documented.[44] In human studies, a reduction in messenger RNA (mRNA) phospholamban levels has been reported,[39,45,46] but absolute protein levels appear to be unchanged in severe hypertrophy and/or failure.[39,46,47] This may represent an imbalance in the transcription and/or translation rates of phospholamban in severe hypertrophy and/or failure. Nevertheless, if SERCA-2 levels decrease without a comparable change in phospholamban expression, alterations in the stoichiometry between these proteins can result. Using transfection techniques, Hajjar and colleagues[48] overexpressed the phospholamban protein in cardiac myocytes. The increased ratio of phospholamban to SERCA-2 resulted in slowed Ca^{2+} re-uptake into the

SR and increased resting Ca^{2+} concentrations. These studies demonstrate the importance of the phospholamban/SERCA-2 stoichiometric relationship in maintaining SR Ca^{2+} re-uptake and intracellular Ca^{2+} concentrations, a relationship that may be altered in the setting of severe hypertrophy and/or failure.

The slower Na^+/Ca^{2+} exchanger also participates in the extrusion of cytosolic Ca^{2+} during active relaxation. There appears to be up-regulation of the Na^+/Ca^{2+} exchanger gene expression and activity in hypertrophy and/or failure.[49-52] The up-regulation of this protein may initially serve as a compensatory mechanism resulting from the reduction of SERCA-2 function. This may eventually result in an overall reduction in the amount of cytosolic Ca^{2+} available for SR uptake and subsequent release for excitation-contraction coupling.

SR re-uptake of cytosolic Ca^{2+} is an energy-dependent process.[4] Therefore increased intracellular Ca^{2+} levels will require increased hydrolysis of ATP for resequestration and maintenance of a normal resting cytosolic Ca^{2+} concentration. In hypertrophied myocardium, reduced basal levels of high-energy phosphates such as ATP have been reported.[53] This reduction in intrinsic levels of high-energy phosphates will also impede energy-dependent resequestration of Ca^{2+} and thereby cause increased cytosolic Ca^{2+} levels in hypertrophy and/or failure.[54] Hypothermic, hyperkalemic cardioplegic arrest is associated with an increase in intracellular Ca^{2+}.[55-57] For example, in an in vitro model of cardioplegic arrest and rewarming, increased intracellular Ca^{2+} levels have been recorded, which persisted in the early reperfusion period (Fig 3).[55] Furthermore, additional studies with cardioplegic arrest and rewarming have reported a prolongation of the isovolumic pressure decline,[58,59] indicative of abnormalities in myocyte active relaxation. Thus conventional cardioplegic arrest may alter Ca^{2+} homeostatic mechanisms, which can persist in the early reperfusion period. These alterations in Ca^{2+} homeostasis may exacerbate pre-existing abnormalities in severe hypertrophy and/or failure which, in turn, would contribute to LV dysfunction in the early postoperative period.

Myocyte receptor systems

A number of sarcolemmal receptor systems are affected with the development of hypertrophy and/or failure.[60-62] This review will focus on the prototypical β-adrenergic receptor (β-AR) system as it is the receptor system most often pharmacologically manipulated in the early postoperative setting. Under ideal circumstances, intracellular phosphorylation targets after β-AR stimulation are the L-type Ca^{2+} channel, phospholamban, and troponin I of the contractile apparatus. Thus alteration in the expression, function, and/or activation of the β-AR system will influence key components of the excitation-contraction coupling process, thereby affecting myocyte contractile function. In hypertrophy and/or failure, a decrease in β-AR density has been reported. For example, Bristow and associates[63] reported a 62% reduction of the β_1 receptor subtype in failing human myocardium. This may be in response to a persistent elevation of circulating catecholamines that can occur in the latter stages of hypertrophy and/or failure.[64,65] In addition, there appears to be a reduction in the ability of existing β_1 receptors to respond to circulating catecholamine levels.[66-68] This has been defined as receptor densensitization.[69-71] This desensitization of available β_1 receptors appears to be multifactorial, which includes alterations both at the level of the receptor and at intracellular transduction pathways. Seconds to minutes after β-AR exposure to receptor agonist, phosphorylation of the β-AR by receptor-associated kinases may occur, resulting in receptor uncoupling.[66,69,72] A further downstream mechanism for alterations in β-AR signaling is likely to be due to alterations in the guanine nucleotide–dependent coupling protein (G protein). Although studies do not report a change in the density of the stimulatory G protein in severe hypertrophy and/or failure,[73-75] studies have shown an increase in the density of the inhibitory G protein[76-78] that would result in a reduction of adenylate cyclase activity. In addition, an apparent desensitization of adenylate cyclase has been reported, which would further diminish β-AR–mediated contractility.[79] Thus, although a number of defects exist in the β-AR with severe hypertrophy and/or failure, the end result will be diminished cyclic adenosine monophosphate production which, in turn, will influence contractile performance in the setting of hypertrophy and/or failure.

Increased sympathetic activity and the resultant increase in plasma catecholamines commonly occurs in the cardiac surgical setting and may contribute to β-AR desensitization.[80-82] Using atrial myocardial specimens, Booth and colleagues[83] reported diminished adenylate cyclase activity after cardiopulmonary bypass with β-AR stimulation. In an isolated myocyte system of hyperkalemic cardioplegic arrest, reduced contractile response to the β-AR system has been demonstrated after reperfusion and rewarming.[55,84] A representative contraction profile of isolated myocytes under normothermic conditions and after simulated cardioplegic arrest is shown in Fig 4. Although exposure to the β-receptor agonist isoproterenol resulted in an overall increase in myocyte contractility, this response was blunted after cardioplegic arrest and rewarming. This is indicative of

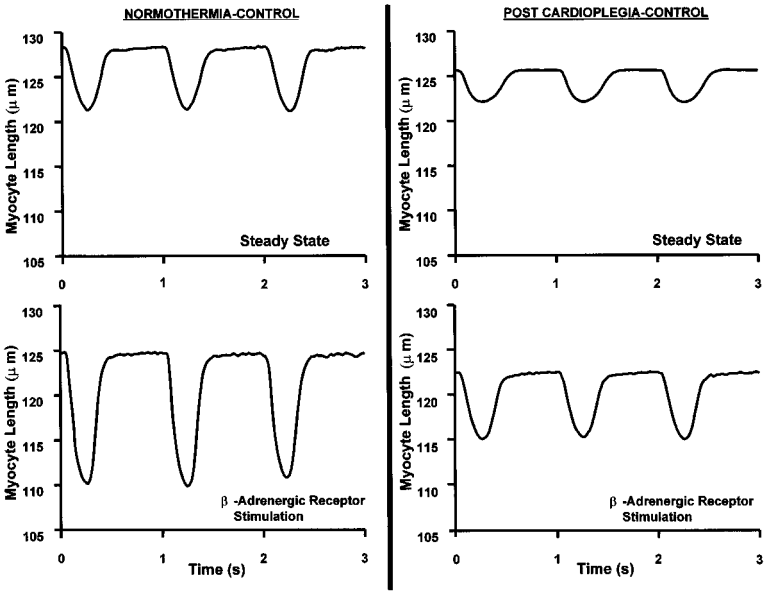

Fig 4. A representative contractile profile of a control myocyte under normothermic conditions *(left panel)* and after cardioplegic arrest *(right panel).* Myocytes were stimulated at 1 Hz by means of methods described previously.[16,55,84] In normothermic control myocytes, a robust increase in contractile performance was observed after β-receptor stimulation. After hypothermic, cardioplegic arrest, steady-state myocyte contractility was reduced in comparison with normothermic control conditions. Furthermore, β-adrenergic stimulation after cardioplegia resulted in a blunted contractile response. These results indicate alterations in the β-adrenergic signaling pathway after hypothermic cardioplegic arrest. Thus the reduction in the β-adrenergic response that may exist in hypertrophied and/or failing myocardium may be heightened and/or exacerbated in the cardiac surgical setting.

a reduction in β-AR response to receptor stimuli. Thus the diminished β-AR response that may exist in patients with pre-existing hypertrophy and/or failure may be further reduced in the setting early after cardiac surgery.

Myocyte cytoskeleton

The extramyofilament cytoskeleton of the myocyte provides a structural framework for myofibrillar assembly and contributes to sarcomere alignment and the transduction of sarcomere shortening into overall myocyte shortening. The cytoskeletal network ranges from the largest components, microtubules (25 nm), to endosarcomeric proteins at a size of 2 nm. It has been demonstrated that increased β-tubulin occurs in the hypertrophied myocyte isolated from patients and animal models of severe pressure overload in the adult.[85] This increase in microtubule density has been reported with severe hypertrophy to be a compensatory response for heightened stress placed on the myocardium. Furthermore, the increased density of the microtubule network within the myocyte may actually impair contractile performance in hypertrophy and/or failure.[86,87] These studies have provided evidence that increased microtubule network density could cause a viscous resistive load impeding sarcomere shortening. Indeed, maneuvers that alter microtubule stability at the level of the isolated myocyte influence contractility. For example, when microtubules are depolymerized in pressure-overload hypertrophy, contractility returns to normal.[85] Of interest, hypothermic exposure caused microtubule reorganization in hypertrophied and normal myocytes, which affects contractile function.[86] When pressure-overloaded myocytes were exposed to profound hypothermic conditions, microtubule depolymerization occurred. With subsequent warming, the contractile function of the hypertrophied myocytes was normalized, indicative of an improvement in contractile function (Fig 5). Thus hypothermia and cardioplegic arrest in hypertrophied myocardium may influence microtubule stability and thereby contractile performance with reperfusion and rewarming. However, these issues remain speculative and warrant further study.

Congestive heart failure

Congestive heart failure (CHF) is a constellation of signs and symptoms including peripheral and pulmonary edema, fatigue on minimal exertion, and shortness of breath. CHF is an insidious disease process that progresses over time and, therefore, should be considered a chronic disease state. After an initial myocardial

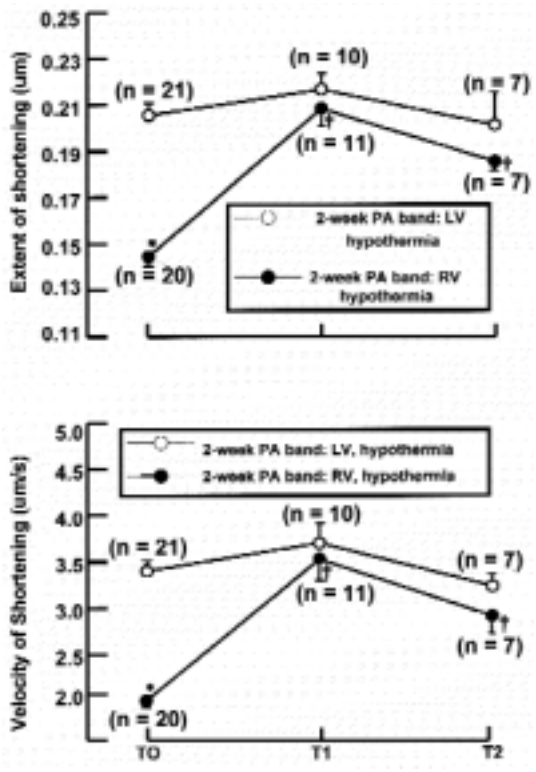

Fig 5. The effects of hypothermia on the extent *(top)* and velocity *(bottom)* of sarcomere shortening in normal left ventricular *(LV)* and hypertrophied right ventricular *(RV)* feline cardiac myocytes. After hypothermic exposure (<10°C) and rewarming, the extent and velocity of sarcomere shortening in hypertrophied myocytes was normalized. These changes are associated with alterations in cytoskeletal tubulin polymerization. *PA,* Pulmonary artery. (Reprinted with permission from Tsutsui H, Ishihara K, Cooper G IV. Cytoskeletal role in the contractile dysfunction of hypertrophied myocardium. Science 1993;260:682-7, copyright 1993 American Association for the Advancement of Science.)

insult, mechanisms are invoked that attempt to compensate for the intrinsic decline in LV myocardial contractility. Early compensatory symptoms may be minimal or nonexistent in these initial stages of the CHF process. However, sustained activation of these compensatory mechanisms can actually contribute to and/or accelerate the progression of CHF. One of the more notable compensatory response mechanisms in the CHF process is the activation of neurohormonal axes.[88-90] These include the sympathetic adrenergic system, the renin-angiotensin-aldosterone system, and the endothelin system.

Activation of the sympathetic adrenergic system is a hallmark feature of disease progression in CHF.[91-93] In the initial stages of CHF, increased catecholamine production has been postulated to serve as a compensatory mechanism for the intrinsic reduction in LV myocardial contractile performance. Plasma catecholamines rise in a temporal manner in CHF, and significantly elevated levels have been shown to be a prognostic index of disease severity and progression.[94,95] For example, a relationship exists between plasma catecholamines and survival.[96,97] Prolonged exposure to elevated plasma catecholamines and, in turn, chronic activation of the β-AR system can result in a number of deleterious consequences. As discussed earlier in this review, sustained β-AR activation can result in β-AR desensitization and subsequent down-regulation of the β_1 receptor.[66-71] The effects of sympathetic adrenergic activation may contribute to LV myocardial remodeling and hypertrophy and, therefore, structurally contribute to CHF. In addition, excessive local production and/or release of norepinephrine concentrations can be deleterious to cardiac myocyte viability. Isolated cardiac myocyte studies have shown concentration-dependent effects of norepinephrine on cell death possibly through apoptosis.[98,99] Finally, the activation of the sympathetic adrenergic system enhances the production and release of other potent vasoactive peptides, particularly angiotensin II and endothelin-1.[96,100]

Since increased sympathetic adrenergic activity was viewed as an appropriate compensatory mechanism, early attempts were made to augment these effects through direct activation of the β-AR by oral agonists or phosphodiesterase inhibitors, which increased the levels of circulating adenosine monophosphate.[101,102] The rationale was to increase intrinsic myocardial contractility and thereby improve overall LV ejection performance. Short-term treatment with β-AR agonists or phosphodiesterase inhibitors resulted in an improvement in LV function and symptoms.[103] However, these effects lessened as treatment continued, and long-term clinical trails demonstrated increased mortality after several months of therapy.[104,105] These observations led to the hypothesis that overstimulation of the β-AR system may be deleterious and that β-AR blockade may be beneficial. This concept emerged slowly since it appeared counterintuitive to inhibit a mechanism that positively influenced myocardial contractility.[106] In fact, the acute response after initiation of a β-AR antagonist was the predicted negative inotropic effect and transient worsening of CHF symptoms.[107] However, studies have demonstrated that long-term treatment with β-AR antagonists resulted in improved LV ventricular function, as well as reduced mortality.[108] Most recently, the nonselective β-AR antagonist carvedilol has been approved for the treatment of mild to moderate CHF.[109-111] In addition to directly demonstrating

that prolonged sympathetic activation contributes to the CHF process, the institution of β-AR antagonists in the pharmacologic armamentarium of patients with CHF may present a new challenge in intraoperative management after cardiac surgery.

Activation of the renin-angiotensin-aldosterone system is also a hallmark of severe chronic CHF.[112] Renin cleaves the angiotensin proform, angiotensinogen, to angiotensin I. Angiotensin II is then formed through the cleavage of angiotensin I by angiotensin-converting enzyme, or ACE. Angiotensin II acts both as a direct vasoconstrictor of vascular smooth muscle cells and in conjunction with the sympathetic adrenergic system to increase vascular tone.[113-115] Angiotensin II can cause increased circulating volume through fluid and sodium retention.[113,116,117] Finally, angiotensin II appears to have trophic and mitogenic effects at the cellular level.[118,119]

In patients with CHF who have systolic dysfunction, the administration of ACE inhibitors reduces afterload and LV wall stress.[120-123] These beneficial loading effects of ACE inhibition result in increased LV ejection performance. ACE inhibitors also promote sodium excretion through the reduction in aldosterone and vasopressin production. In addition, ACE inhibitors may influence myocardial remodeling by blocking the mitogenic effects of angiotensin II on cardiac myocytes and fibroblasts.[124-127] Several clinical CHF trials have demonstrated that ACE inhibition reduced overall mortality, primarily through a reduction in the progression of the CHF disease process.[128-131] Thus ACE inhibition provides beneficial effects on LV function and myocardial remodeling and has become the standard of treatment for patients with CHF.

In patients with CHF, aldosterone levels may increase by over 20-fold compared with normal levels.[132] A recent clinical study examined the effects of the aldosterone receptor antagonist, spironolactone, in the setting of CHF.[133] The results from this study demonstrated an additive beneficial effect when spironolactone was used in conjunction with standard ACE inhibitor therapy.[133] Thus new pharmacologic strategies are becoming available that can selectively modulate specific neurohormonal receptor systems and may have particular relevance in patients presenting with severe hypertrophy and/or CHF for cardiac surgery.

The endothelins are a family of bioactive peptides consisting of three isoforms: endothelin-1, endothelin-2, and endothelin-3, with endothelin-1 being the most potent and biologically active.[134] Specifically, through the activation of the endothelin A receptor subtype, endothelin-1 can cause significant and prolonged constriction of vascular smooth muscle.[135] Thus endothelin-1 is involved in the regulation of systemic and pulmonary vascular resistance properties. The vasoconstrictive properties of endothelin-1 are exemplified by clinical studies that have demonstrated that endothelin-1 receptor blockade significantly reduces systemic vascular resistance in hypertension.[136] Moreover, the profound effects of endothelin-1 with respect to pulmonary vascular resistance were demonstrated by the involvement of this bioactive peptide in the setting of primary pulmonary hypertension.[137] In the setting of CHF, endothelin-1 production is increased and, as such, has been implicated to directly contribute to the progression and/or exacerbation of the disease process.[138] In fact, a nonselective endothelin receptor antagonist, bosentan, has been successfully used in patients with CHF, resulting in a reduction in systemic and pulmonary vascular resistance.[139,140]

Endothelin-1 receptor stimulation activates a number of intracellular signaling pathways that continue to be an area of active investigation.[141-144] The downstream events of endothelin-1 stimulation with respect to the myocyte are likely to involve activation the Na^+/H^+ exchanger as well as several Ca^{2+} regulatory processes.[145-147] The end result of endothelin-1 receptor stimulation in normal myocytes is an increase in contractile performance. However, in the context of LV failure, endothelin-1 receptor activation results in a reduction in contractility.[148,149] The negative inotropic effects of endothelin-1 with pre-existing LV failure is likely the result of the exacerbation of intrinsic defects in Ca^{2+} homeostasis. Thus, in patients with CHF admitted for cardiac surgery, the systemic and myocardial effects of endothelin-1 may have particular importance.

Future directions

An important consideration in preventing further alterations in ionic currents and Ca^{2+} homeostatic mechanisms in the hypertrophied and/or failing myocardium would be to alter extracellular stimuli that could influence these intracellular processes. For example, the institution of cardiopulmonary bypass results in the activation of several neurohormonal systems, including the sympathetic adrenergic system, as well as the synthesis of bioactive peptides that persist in the postoperative period.[150-152] Heightened sympathetic adrenergic activity and the resulting release of catecholamines with respect to the effects on the β-AR system have been discussed earlier in this review. With respect to bioactive peptides, plasma levels of endothelin-1 have been shown to be increased during cardiopulmonary bypass, and these elevations persist into the postoperative period.[152] Thus, in patients with pre-existing hypertrophy and/or CHF, increased endothelin-1 levels in the setting of cardiopulmonary bypass may directly contribute to LV

myocardial dysfunction by direct negative inotropic effects. More recently, endothelin-1 receptor antagonists have been developed and successfully used in patients with LV pump dysfunction.[153,154] Thus new pharmacologic strategies are becoming available which can selectively modulate specific receptor systems that may have particular relevance in patients presenting for cardiac surgery with severe hypertrophy and/or CHF.

Summary

As the number of patients with pre-existing myocardial hypertrophy and/or CHF increases, the elucidation of mechanisms that potentially contribute to LV dysfunction after cardiac surgery is warranted. The results from recently performed studies, some of which have been reviewed here, suggest that underlying contributory factors for the exacerbation of LV dysfunction in patients with pre-existing hypertrophy and/or failure in the postoperative cardiac setting are changes in ionic currents and Ca^{2+} homeostasis. Therefore strategies that are focused on these ionic defects in LV hypertrophy and/or failure may have therapeutic benefit in the cardiac surgical setting. For example, the induction of myocardial electrical quiescence and cardioplegic arrest has been successfully achieved through the use of potassium channel openers that maintain the negative resting membrane potential of the myocyte.[55] In isolated myocyte systems, the use of potassium channel openers has been demonstrated to prevent intracellular Ca^{2+} accumulation during the cardioplegic arrest period, which translated into reduced cytosolic Ca^{2+} levels with reperfusion and rewarming.[55] Furthermore, the use of potassium channel openers in the intact LV has been demonstrated to maintain indices of LV ejection performance with reperfusion and rewarming in the setting of cardiopulmonary bypass.[155] Thus strategies that facilitate cardioplegic arrest without detrimental effects on ionic currents and intracellular Ca^{2+} dynamics may have important implications with pre-existing LV hypertrophy and/or failure.

REFERENCES

1. Weisel RD. Myocardial stunning after coronary bypass surgery. J Card Surg 1993;8:242-4.
2. Mangano DT. Cardiovascular morbidity and CABG surgery—a perspective: epidemiology, costs, and potential therapeutic solutions. J Card Surg 1995;10:366-8.
3. Dalrymple-Hay MJ, Alzetani A, Aboel-Nazar S, Haw M, Livesey S, Monro J. Cardiac surgery in the elderly. Eur J Cardiothoracic Surg 1999;15:61-6.
4. Katz AM. Physiology of the heart. New York: Raven Press, 1992.
5. Kleiman RB, Houser SR. Outward currents in normal and hypertrophied feline ventricular myocytes. Am J Physiol 1989; 256:H1450-61.
6. Kleiman RB, Houser SR. Outward currents in hypertrophied feline ventricular myocytes. Prog Clin Biol Res 1990;334:65-83.
7. Priebe L, Beuckelmann DJ. Simulation study of cellular electric properties in heart failure. Circ Res 1998;82:1206-23.
8. Furukawa T, Bassett AL, Furukawa N, Kimura S, Myerburg RJ. The ionic mechanism of reperfusion-induced early after depolarizations in feline left ventricular hypertrophy. J Clin Invest 1993;91:1521-31.
9. Nuss HB, Marban E, Johns DC. Overexpression of a human potassium channel suppresses cardiac hyperexcitability in rabbit ventricular myocytes. J Clin Invest 1999;103:889-96.
10. Tomaselli GF, Beuckelmann DJ, Calkins HG, Berger RD, Kessler PD, Lawrence JH, et al. Sudden cardiac death in heart failure: the role of abnormal repolarization. Circulation 1994; 90:2534-9.
11. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. Circulation 1983;67:1356-67.
12. Ellingsen O, Holthe MR, Svindland A, Aksnes G, Serjersted OM, Ilebekk A. Na,K-pump concentration in hypertrophied human hearts. Eur Heart J 1994;15:1184-90.
13. Spinale FG, Clayton C, Tanaka R, Fulbright BM, Mukherjee R, Schulte BA, et al. Myocardial Na+,K(+)-ATPase in tachycardia induced cardiomyopathy. J Mol Cell Cardiol 1992;24:277-94.
14. Schwinger RH, Wang J, Frank K, Muller-Ehmsen J, Brixius K, McDonough AA, et al. Reduced sodium pump alpha 1, alpha 3, and beta-1 isoform protein levels and Na+,K+-ATPase activity but unchanged Na+-Ca2+ exchanger protein levels in human heart failure. Circulation 1999;99:2105-12.
15. Anderson DR, Stephenson LW, Edmunds LH. Management of complications of cardiopulmonary bypass: complications of organ systems. In: Waldhausen JA, Orringer MB, editors: Complications in cardiothoracic surgery. St. Louis: Mosby-Year Book; 1991.
16. Mukherjee R, Hewett KW, Walker JD, Basler CG, Spinale FG. Changes in L-type calcium channel abundance and function during the transition to pacing-induced congestive heart failure. Cardiovasc Res 1998;37:432-44.
17. Mukherjee F, Spinale FG. L-type calcium channel abundance and function with cardiac hypertrophy and failure: a review. J Mol Cell Cardiol 1998;30:1899-916.
18. Mewes T, Ravens U. L-type calcium currents of human myocytes from ventricle of non-failing and failing hearts and from atrium. J Mol Cell Cardiol 1994;26:1307-20.
19. Colston JT, Kumar P, Chambers JP, Freeman GL. Altered sarcolemmal calcium channel density and Ca(2+)-pump ATPase activity in tachycardia heart failure. Cell Calcium 1994;5:349-56.
20. Wagner JA, Sax FL, Weisman HF, Porterfield J, McIntosh C, Weisfeldt ML, et al. Calcium-antagonist receptors in the atrial tissue of patients with hypertrophic cardiomyopathy. N Engl J Med 1989;320:755-61.
21. Beuckelmann DJ, Naubauer M, Erdmann E. Intracellular calcium handling in isolated ventricular myocytes from patients with terminal heart failure. Circulation 1992;85:1046-55.
22. Brillantes AM, Allen P, Takahashi T, Izumo S, Marks AR. Differences in cardiac calcium release channel (ryanodine receptor) expression in myocardium from patients with end-stage heart failure caused by ischemic versus dilated cardiomyopathy. Circ Res 1992;71:18-26.
23. Go LO, Moschella MC, Watras J, Handa KK, Fyfe BS, Marks

AR. Differential regulation of two types of intracellular calcium release channels during end-stage heart failure. J Clin Invest 1995;96:888-94.

24. D'Agnolo A, Luciani GB, Mazzucco A, Gallucci V, Salviati G. Contractile properties and Ca2+ release activity of the sarcoplasmic reticulum in dilated cardiomyopathy. Circulation 1992;85:518-25.
25. Nimer LR, Needleman DH, Hamilton SL, Krall J, Movsesian MA. Effect of ryanodine on sarcoplasmic reticulum Ca2+ accumulation in nonfailing and failing human myocardium. Circulation 1995;92:2504-10.
26. Lompre AM, Schwartz K, d'Albis A, Lacombe G, Van Thiem N, Swynghedauw B. Myosin isoenzyme redistribution in chronic heart overload. Nature 1979;282:105-7.
27. Nadal-Ginard B, Mahdavi V. Molecular basis of cardiac performance: plasticity of the myocardium generated through protein isoform switches. J Clin Invest 1989;84:1693-700.
28. Dorn GW II, Robbins J, Ball N, Walsh RA. Myosin heavy chain regulation and myocyte contractile depression after LV hypertrophy in aortic-banded mice. Am J Physiol 1994;267: H400-5.
29. Yelmarty RV, Moore RL, Yu FT, Elensky M, Semanchick AM, Cheung JY. Relaxation abnormalities in single cardiac myocytes from renovascular hypertensive rats. Am J Physiol 1992; 262:C980-90.
30. Lowes BD, Minobe W, Abraham WT, Rizeq MN, Bohlmeyer TJ, Quaife RA, et al. Changes in gene expression in the intact human heart: downregulation of alpha-myosin heavy chain in hypertrophied, failing ventricular myocardium. J Clin Invest 1997;100:2315-24.
31. Weiss A, Leinwand LA. The mammalian myosin heavy chain gene family. Ann Rev Cell Dev Biol 1996;12:417-39.
32. Adams JE III, Bodor GS, Davalia-Roman VG, Delmez JA, Apple FS, Ladenson JH, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. Circulation 1993;88: 101-6.
33. Ascione R, Lloyd CT, Gomes WJ, Caputo M, Bryan AJ, Angelini GD. Beating verses arrested heart revascularization: evaluation of myocardial function in a prospective randomized study. Eur J Cardiothorac Surg 1999;15:685-90.
34. Lindner M, Erdmann E, Beuckelmann DJ. Calcium content of the sarcoplasmic reticulum in isolated ventricular myocytes from patients with terminal heart failure. J Mol Cell Cardiol 1998;30:743-9.
35. Gwathmey JK, Copelas L, MacKinnon R, Schoen FJ, Feldman MD, Grossman W, et al. Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. Circ Res 1987;61:70-6.
36. Wexler LF, Lorell BH, Momomura S, Weinberg EO, Ingwall JS, Apstein CS. Enhanced sensitivity to hypoxia-induced diastolic dysfunction in pressure-overload left ventricular hypertrophy in the rat: role of high-energy phosphate depletion. Circ Res 1988;62:766-75.
37. Huddleston CB, Wareing TH, Boucek RJ, Hammon JW Jr. Response of the hypertrophied left ventricle to global ischemia: comparison of hyperkalemic cardioplegic solution with and without verapamil. J Thorac Cardiovasc Surg 1992;103:919-26.
38. de la Bastie D, Levitsky D, Rappaport L, Mercadier JJ, Marotte F, Wisnewsky C, et al. Function of the sarcoplasmic reticulum and expression of its Ca2(+)-ATPase gene in pressure overload-induced cardiac hypertrophy in the rat. Circ Res 1990; 66:554-64.
39. Schwinger RH, Bohm M, Schmidt U, Karczewski P, Bavendiek U, Flesch M, et al. Unchanged protein levels of SERCA II and phospholamban but reduced Ca2+ uptake and Ca(2+)-ATPase activity of cardiac sarcoplasmic reticulum from dilated cardiomyopathy patients compared with patients with nonfailing hearts. Circulation 1995;92:3220-8.
40. Meyer M, Schillinger W, Peiske B, Holubarsch C, Heilmann C, Poisval H, et al. Alterations of sarcoplasmic reticulum proteins in failing dilated cardiomyopathy. Circulation 1995;92:778-84.
41. Hasenfuss G, Reinecke H, Struder R, Meyer M, Pieske B, Holtz J, et al. Relation between myocardial function and expression of sarcoplasmic reticulum Ca(2+)-ATPase in failing and nonfailing human myocardium. Circ Res 1994;75:434-42.
42. Struder R, Reinecke H, Bilger J, Eschenhagen T, Bohm M, Hasenfuss G,. Gene expression of the cardiac Na(+)-Ca(2+) exchanger in end-stage human heart failure. Circ Res 1994;75: 443-53.
43. Dillman WH. Regulation of expression of cardiac sarcoplasmic reticulum proteins under pathophysiological conditions. Mol Cell Biochem 1996;157:125-8.
44. Kiss E, Ball NA, Kranias EG, Walsh RA. Differential changes in cardiac phospholamban and sarcoplasmic reticular Ca(2+)-ATPase protein levels: effects on Ca2+ transport and mechanics in compensated pressure-overload hypertrophy and congestive heart failure. Circ Res 1995;77:759-64.
45. Flesch M, Schwinger RH, Schnabel P, Schiffer F, van Gelder I, Bavendiek U, et al. Sarcoplasmic reticulum Ca2+-ATPase and phospholamban mRNA and protein levels in end-stage heart failure due to ischemic or dilated cardiomyopathy. J Mol Med 1996;74:321-32.
46. Linck B, Boknik P, Eschenhagen T, Muller FU, Neumann J, Nose M, et al. Messenger RNA expression and immunological quantification of phospholamban and SR-Ca(2+)-ATPase in failing and nonfailing human hearts. Cardiovasc Res 1996;31: 625-32.
47. Movsesian MA, Karimi M, Green K, Jones LR. Ca(2+)-transporting ATPase, phospholamban, and calsequestrin levels in nonfailing and failing human myocardium. Circulation 1994; 90:653-7.
48. Hajjar RJ, Schmidt U, Kan JX, Matsui T, Rosenweig A. Adenoviral gene transfer of phospholamban in isolated rat cardiomyocytes: rescue effects of concomitant gene transfer of sarcoplasmic reticulum Ca(2+)-ATPase. Circ Res 1997;81:145-53.
49. Reinecke H, Struder R, Vetter R, Just H, Holtz J, Drexler H. Role of the cardiac sarcolemmal Na(+)-Ca2+ exchanger in end-stage human heart failure. Ann N Y Acad Sci 1996;779:543-5.
50. Reinecke H, Struder R, Vetter R, Holtz J, Drexler H. Cardiac Na+/ Ca2+ exchange activity in patients with end-stage heart failure. Cardiovasc Res 1996;31:48-54.
51. Flesch M, Schwinger RH, Schiffer F, Frank R, Sudkamp M, Kuhn-Regnier F, et al. Evidence for functional relevance of an enhanced expression of the Na(+)-Ca2+ exchanger in failing human myocardium. Circulation 1996;94:992-1002.
52. Yashar PR, Fransua M, Frishman WH. The sodium-calcium ion membrane exchanger: physiologic significance and pharmacologic implications. J Clin Pharmacol 1998;38:393-401.
53. Attarian DE, Jones RN, Currie WD, Hill RC, Sink JD, Olsen CO, et al. Characteristics of chronic left ventricular hypertrophy induced by subcoronary valvular aortic stenosis. I. Myocardial blood flow and metabolism. J Thorac Cardiovasc Surg 1981;81:382-8.

54. Menasche P, Tronc F, Nguyen A, Veyssie L, Demirag M, Lariviere J, et al. Retrograde warm blood cardioplegia preserves hypertrophied myocardium: a clinical study. Ann Thorac Surg 1994;57:1429-34.
55. Dorman BH, Hebbar L, Clair MJ, Hinton RB, Roy RC, Spinale FG. Potassium channel opener–augmented cardioplegia: protection of myocyte contractility with chronic left ventricular dysfunction. Circulation 1997;96(9 Suppl):II253-9.
56. Jovanovic A, Lopez JR, Alekseev AE, Shen WK, Terzic A. Adenosine prevents K+-induced Ca2+ loading: insight into cardioprotection during cardioplegia. Ann Thorac Surg 1998; 65:586-91.
57. Cyran SE, Ditty SE, Baylen BG, Cheung J, LaNoue KF. Developmental differences in the response of cytosolic free calcium to potassium depolarization and cardioplegia in cardiac myocytes. J Mol Cell Cardiol 1992;24:1167-77.
58. Schaff HV, Dombroff R, Flaherty JT, Bulkley BH, Hutchins GM, Goldman RA, et al. Effect of potassium cardioplegia on myocardial ischemia and post arrest ventricular function. Circulation 1978;58:240-9.
59. Flaherty JT, Schaff HV, Goldman RA, Gott VL. Metabolic and functional effects of progressive degrees of hypothermia during global ischemia. Am J Physiol 1979;236:H839-45.
60. Castellano M, Bohm M. The cardiac beta-adrenoceptor–mediated signaling pathway and its alterations in hypertensive disease. Hypertension 1997;29:715-22.
61. Leier CV, Binkley PF, Cody RJ. Alpha-adrenergic component of the sympathetic nervous system in congestive heart failure. Circulation 1990;82(2 Suppl):I68-76.
62. Schriffin EL, Intengan HD, Thibault G, Touyz RM. Clinical significance of endothelin in cardiovascular disease. Curr Opin Cardiol 1997;12:354-67.
63. Bristow MR, Ginsburg R, Umans V, Fowler M, Minobe W, Rasmussen R, et al. Beta-1 and beta-2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. Circ Res 1986;59:297-309.
64. Dzau VJ, Hollenberg NK, Williams GH. Neurohumoral mechanisms in heart failure: role in pathogenesis, therapy, and drug tolerance. Fed Proc 1983;42:3162-9.
65. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. Ann Intern Med 1984;101:370-7.
66. Choi DJ, Koch WJ, Hunter JJ, Rockman HA. Mechanism of beta-adrenergic receptor desensitization in cardiac hypertrophy is increased beta-adrenergic receptor kinase. J Biol Chem 1997; 272:17223-9.
67. Hausdorff WP, Caron MG, Lefkowitz RJ. Turning off the signal: desensitization of beta-adrenergic receptor function. FASEB J 1990;4:2881-9.
68. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS, Lurie K, et al. Decreased catecholamine sensitivity and beta-adrenergic–receptor density in failing human hearts. N Engl J Med 1982;307:205-11.
69. Schwinn DA, Caron MG, Lefkowitz RJ. The beta-adrenergic receptor as a model for molecular structure-function relationships in G-protein–coupled receptors. In: Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE, editors: The heart and cardiovascular system. Scientific foundations. 2nd ed. New York: Raven Press; 1992.
70. Benovic JL, Bouvier M, Caron MG, Lefkowitz RJ. Regulation of adenylyl cyclase–coupled beta-adrenergic receptors. Ann Rev Cell Biol 1998;4:405-28.
71. Lefkowitz RJ, Hausdorff WP, Caron MG. Role of phosphorylation in desensitization of the beta-adrenoceptor. Trends Pharmacol Sci 1990;11:190-4.
72. Bohm M, Flesch M, Schnabel P. Role of G-proteins in altered beta-adrenergic responsiveness in the failing and hypertrophied myocardium. Basic Res Cardiol 1996;91 Suppl 2:47-51.
73. Bohm M, Gierschik P, Jakobs KH, Pieske B, Schnabel P, Ungerer M, et al. Increase of Gi alpha in human hearts with dilated but not ischemic cardiomyopathy. Circulation 1990;82:1249-65.
74. Schnabel P, Bohm M, Gierschik P, Jakobs KH, Erdmann E. Improvement of cholera toxin–catalyzed ADP-ribosylation by endogenous ADP-ribosylation factor from bovine brain provides evidence for an unchanged amount of Gs alpha in failing human myocardium. J Mol Cell Cardiol 1990;22:73-82.
75. Feldman AM, Cates AE, Veazey WB, Hershberger RE, Bristow MR, Baughman KL, et al. Increase of the 40,000-mol wt pertussis toxin substrate (G protein) in the failing human heart. J Clin Invest 1988;82:189-97.
76. Neumann J, Schmitz W, Scholtz H, von Meyerinck L, Doring V, Kalmar P. Increase in myocardial Gi-proteins in heart failure. Lancet 1988;2:936-7.
77. Eschenhagen T, Mende U, Nose M, Schmitz W, Scholtz H, Haverich A, et al. Increased messenger RNA level of inhibitory G protein alpha subunit Gi alpha-2 in human end-stage heart failure. Circ Res 1992;70:688-96.
78. Marzo KP, Frey MJ, Wilson JR, Liang BT, Manning DR, Lanoce V, et al. Beta-adrenergic receptor-G protein-adenylate cyclase complex in experimental canine congestive heart failure produced by rapid ventricular pacing. Circ Res 1991;69:1546-56.
79. Tanaka R, Fulbright BM, Mukherjee R, Burchell SA, Crawford FA, Zile MR, et al. The cellular basis for the blunted response to beta-adrenergic stimulation in supraventricular tachycardia-induced cardiomyopathy. J Mol Cell Cardiol 1993;25:1215-33.
80. Schrantz D, Droege A, Broede A, Brodermann G, Schafer E, Oelert H, et al. Uncoupling of human cardiac beta-adrenoceptors during cardiopulmonary bypass with cardioplegic cardiac arrest. Circulation 1993;87:422-6.
81. Tan CK, Glisson SN, El-Etr AA, Ramakrishnaiah KB. Levels of circulating norepinephrine and epinephrine before, during, and after cardiopulmonary bypass in man. J Thorac Cardiovasc Surg 1976;71:928-31.
82. Reves JG, Karp RB, Buttner EE, Tosone S, Smith LR, Samuelson PN, et al. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 1982;66:49-55.
83. Booth JV, Landolfo KP, Chesnut LC, Bennett-Guerrero E, Gerhardt MA, Atwell DM, et al. Acute depression of myocardial beta-adrenergic receptor signaling during cardiopulmonary bypass: impairment of the adenylyl cyclase moiety. Duke Heart Center Perioperative Desensitization Group. Anesthesiology 1998;89:602-11.
84. Houck WV, Kribbs SB, Zellner JL, Doscher MA, Joshi JD, Crawford FA Jr, et al. Normothermic versus hypothermic hyperkalemic cardioplegia: effects in myocyte contractility. Ann Thorac Surg 1998;65:1279-83.
85. Tsutsui H, Tagawa H, Kent RL, McCollam PL, Ishihara K, Nagatsu M, et al. Role of microtubules in contractile dysfunction of hypertrophied cardiocytes. Circulation 1994;90:533-55.

86. Tsutsui H, Ishihara K, Cooper G IV. Cytoskeletal role in the contractile dysfunction of hypertrophied myocardium. Science 1993;260:682-7.
87. Tagawa H, Wang N, Narishige T, Ingber DE, Zile MR, Cooper G IV. Cytoskeletal mechanics in pressure-overload cardiac hypertrophy. Circ Res 1997;80:281-9.
88. Cohn JN. The management of chronic heart failure. N Engl J Med 1996;335:490-8.
89. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. Am J Cardiol 1978;41:233-43.
90. Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. Am J Cardiol 1982;49:1659-66.
91. Mann DL. Mechanisms and models in heart failure: a combinatorial approach. Circulation 1999;100:999-1008.
92. Eishenhofer G, Friberg P, Rundqvist B, Quyyumi AA, Lambert G, Kaye DM, et al. Cardiac sympathetic nerve function in congestive heart failure. Circulation 1996;93:1667-76.
93. Bristow MR The adrenergic system in heart failure. N Engl J Med 1984;311:850-1.
94. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 1999;341:577-85.
95. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819-23.
96. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730-6.
97. Packer M, Lee WH, Kessler PD, Gottlieb SS, Bernstein JL, Kukin ML. Role of neurohormonal mechanism in determining survival in patients with severe chronic heart failure. Circulation 1987;75(Suppl):IV80-92.
98. Mann DL, Kent RL, Parson B, Cooper G IV. Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992;85:790-804.
99. Communal C, Singh K, Pimentel DR, Colucci WS. Norepinephrine stimulates apoptosis in adult rat ventricular myocytes by activation of the beta-adrenergic pathway. Circulation 1998;98:1329-34.
100. Kohno M, Murakawa K, Yokokawa K, Yasunari K, Horio T, Kurihara N, Takeda T. Production of endothelin by cultured porcine endothelial cells: modulation by adrenaline. J Hypertens Suppl 1989;6:S130-1.
101. Movsesian MA. Beta-adrenergic receptor agonists and cyclic nucleotide phosphodiesterase inhibitors: shifting the focus from inotropy to cyclic adenosine monophosphate. J Am Coll Cardiol 1999;34:318-24.
102. Klamerus KJ. Current concepts in clinical therapeutics: congestive heart failure. Clin Pharmacol 1986;5:481-98.
103. Shipley JB, Hess ML. Inotropic therapy for the failing myocardium. Clin Cardiol 1995;18:615-9.
104. Packer M. Is activation of the sympathetic nervous system beneficial or detrimental to the patient with chronic heart failure? Lessons learned from clinical trials with beta-adrenergic agonists and antagonists. J Cardiovasc Pharmacol 1989;14(Suppl 5): S38-43.
105. Lambertz H, Meyer J, Erbel R. Long-term hemodynamic effects of prenalterol in patients with severe congestive heart failure. Circulation 1984;69:298-305.
106. Pepper GS, Lee RW. Sympathetic activation in heart failure and its treatment with beta-blockade. Arch Intern Med 1999;159: 225-34.
107. Binkley PF, Lewe RF, Lima JJ, Al-Awwa A, Unverferth DV, Leier CV. Hemodynamic-inotropic response to beta-blocker with intrinsic sympathomimetic activity in patients with congestive cardiomyopathy. Circulation 1986;74:1390-8.
108. Krum H. Beta-blockers in heart failure. The “new wave” of clinical trials. Drugs 1999;58:203-10.
109. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349-55.
110. Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol 1995;25:1225-31.
111. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation 1996;94:2793-9.
112. Benedict CR, Weiner DH, Johnstone DE, Bourassa MG, Ghali JK, Nicklas J, et al. Comparative neurohormonal responses in patients with preserved and impaired left ventricular ejection fraction: results of the Studies of Left Ventricular Dysfunction (SOLVD) Registry. The SOLVD Investigators. J Am Coll Cardiol 1993;22:146A-53A.
113. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation 1998;97:1411-20.
114. Folkow B, Johansson B, Mellander S. The comparative effects of angiotensin and noradrenaline on consecutive vascular sections. Acta Physiol Scand 1961;53:99-104.
115. Zimmerman BG, Sybertz EJ, Wong PC. Interaction between sympathetic and renin-angiotensin system. J Hypertens 1984;2: 581-7.
116. Biron P, Koiw E, Nowaczynski W. The effects of intravenous infusions of valine-5 angiotensin II and other pressor agents on urinary electrolytes and corticoids including aldosterone. J Clin Invest 1961;60:338-47.
117. Padfield PL, Morton JJ. Effects of angiotensin II on arginine-vasopressin in physiological and pathological situations in man. J Endocrinol 1977;74:251-9.
118. Daeman MJ, Lombardi DM, Bosman FT, Schwartz SM. Angiotensin II induces smooth muscle proliferation in the normal and injured rat arterial wall. Circ Res 1991;68:450-6.
119. Itoh H, Mukoyama M, Pratt RE, Gibbons GH, Dzau VJ. Multiple autocrine growth factors modulate vascular smooth muscle cell growth response to angiotensin II. J Clin Invest 1993;91:2268-74.
120. Gavras H, Faxon DP, Berkoben J, Brunner HR, Ryan TJ. Angiotensin converting enzyme inhibition in patients with congestive heart failure. Circulation 1978;58:770-6.
121. Davis R, Ribner HS, Keung E, Sonnenblick EH, LeJemtel TH. Treatment of chronic congestive heart failure with captopril, an oral inhibitor of angiotensin-converting enzyme. N Engl J Med 1979;301:117-21.

122. Dzau VJ, Colucci WS, Williams GH, Curfman G, Meggs L, Hollenberg NK. Sustained effectiveness of converting-enzyme inhibition in patients with severe congestive heart failure. N Engl J Med 1980:302:1373-9.
123. Levine TB, Franciosa JA, Cohn JN. Acute and long-term response to an oral converting-enzyme inhibitor, captopril, in congestive heart failure. Circulation 1980;62:35-41.
124. Vaughan DE, Pfeffer MA. Angiotensin converting enzyme inhibitors and cardiovascular remodelling. Cardiovasc Res 1994;28:159-65.
125. Dahlof B. Effects of angiotensin II blockade on cardiac hypertrophy and remodelling: a review. J Hum Hypertens 1995; Suppl 5:S37-44.
126. Grohe C, Kahlert S, Lobbert K, Neyses L, van Eickels M, Stimpel M, et al. Angiotensin converting enzyme inhibition modulates cardiac fibroblast growth. J Hypertens 1998;16:377-84.
127. van Eickels M, Grohe C, Lobbert K, Stimpel M, Vetter H. Angiotensin converting enzyme inhibitors block mitogenic signalling pathways in rat cardiac fibroblasts. Naunyn Schmiedebergs Arch Pharmacol 1999;359:394-9.
128. Effects of enalapril on mortality in severe congestive heart failure: results on the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316:1429-35.
129. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325:293-302.
130. Effects of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993;342:821-8.
131. Kober L, Torp-Pedersen C, Carlsen HE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995;333:1670-6.
132. Laragh JH. Hormones and the pathogenesis of congestive heart failure: vasopressin, aldosterone, and angiotensin II: further evidence for renal-adrenal interaction from studies in hypertension and cirrhosis. Circulation 1962;25:1015-23.
133. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.
134. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 1988;332:411-5.
135. Rubanyi GM, Polokoff MA. Endothelins: molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. Pharmacol Rev 1994;46:325-415.
136. Schiffrin EL. Endothelin and endothelin antagonists in hypertension. J Hypertens 1998;16:1891-5.
137. Cacoub P, Dorent R, Maistre G, Nataf P, Carayon A, Piette C, et al. Endothelin-1 in primary pulmonary hypertension and the Eisenmenger syndrome. Am J Cardiol 1993;71:448-50.
138. McMurray JJ, Ray SG, Abdullah I, Dargie HJ, Morton JJ. Plasma endothelin in chronic heart failure. Circulation 1992; 85:1374-9.
139. Sutsch G, Bertel O, Kiowski W. Acute and short-term effects of the nonpeptide endothelin-1 receptor antagonist bosentan in humans. Cardiovasc Drugs Ther 1997;10:717-25.
140. Kiowski W, Sutsch G, Hunziker P, Muller P, Kim J, Oechslin E, et al. Evidence for endothelin-1–mediated vasoconstriction in severe chronic heart failure. Lancet 1995;346:732-6.
141. Neylon CB. Vascular biology of endothelin signal transduction. Clin Exp Pharmacol Physiol 1999;26:149-53.
142. Goldie RG. Endothelin in health and disease: an overview. Clin Exp Pharmacol Physiol 1999;26:145-8.
143. Meyer M, Lenhart S, Pieke B, Schlottauer K, Munk S, Holubarsch C, et al. Influence of endothelin 1 on human atrial myocardium—myocardial function and subcellular pathways. Basic Res Cardiol 1996;91:86-93.
144. Sokolovsky M. Endothelins and sarafotoxins: physiological regulation, receptor subtypes and transmembrane signaling. Pharmacol Ther 1992;54:129-49.
145. Kramer BK, Smith TW, Kelley RA. Endothelin and increased contractility in adult rat ventricular myocytes: role of intracellular alkalosis induced by activation of the protein kinase C-dependent Na(+)-H(+) exchanger. Circ Res 1991;68:269-79.
146. Simonson MS, Dunn MJ. Endothelin. Pathways of transmembrane signaling. Hypertension 1990;15(2 Suppl):I5-12.
147. Sokolovsky M. Endothelin receptor subtypes and their role in transmembrane signaling mechanisms. Pharmacol Ther 1995; 68:435-71.
148. Thomas PB, Liu EC, Webb ML, Mukherjee R, Hebbar L, Spinale FG. Exogenous effects and endogenous production of endothelin in cardiac myocytes: potential significance in heart failure. Am J Physiol 1996;271:H2629-37.
149. Onishi K, Ohno M, Little WC, Cheng CP. Endogenous endothelin-1 depresses left ventricular systolic and diastolic performance in congestive heart failure. J Pharmacol Exp Ther 1999;288:1214-22.
150. Zellner JL, Kribbs SB, Dorman BH, Spinale FG. Cardiopulmonary bypass in a gravid patient: perioperative changes in endothelin levels. Ann Thorac Surg 1998;66:268-70.
151. St Rammos K, Koullias GJ, Hatzibougias JD, Argyrakis NP, Panagopoulos PG. Plasma endothelin-1 levels in adult patients undergoing coronary revascularization. Cardiovasc Surg 1996; 4:808-12.
152. Philbin DM. Endocrine response to cardiopulmonary bypass. Mt Sinai J Med 1985;52:508-10.
153. Sutsch G, Kiowski W, Yan XW, Hunziker P, Christen S, Strobel W, et al. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. Circulation 1998;98:2262-8.
154. Kirchengast M, Munter K. Endothelin-1 and endothelin receptor antagonists in cardiovascular remodeling. Proc Soc Exp Biol Med 1999;221:312.
155. Jayawant AM, Stephenson ER Jr, Matte GS, Prophet GA, LaNoue KF, Griffith JW, et al. Potassium-channel opener cardioplegia is superior to St. Thomas' solution in the intact animal. Ann Thorac Surg 1999;68:67-74.